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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,665	09/28/2000	Sudhirdas K. Prayaga	15966-572	8095

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ART UNIT	PAPER NUMBER
1632	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/672,665	Prayaga
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 17, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4, 23, 24, 29, and 32* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 23, 24, 29, and 32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response received on 12/17/02 has been entered. Claims 5-22, 25-28, 30, 31, 33-35, and 36-43 have been canceled. Claims 1-4, 23-24, 29, and 32 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 1-4, 23-24, 29, 32, 35, and 42 under 35 U.S.C. 112, first paragraph, for lack of written description is maintained. Applicant's arguments and claim amendments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant has amended claim 1 to recite an isolated polypeptide comprising an amino acid sequence of SEQ ID NO:2. Claims 2 has been amended to recite the polypeptide of claim 1 that is a naturally occurring allelic variant of the sequence of SEQ ID NO:2. Please note that claims 1-4, and 23-24, 29, and 32 have been newly rejected under 35 U.S.C. 112, second paragraph, for indefiniteness, see below. Claim 1, as amended, comprises an amino acid sequence of SEQ ID NO:2. Based on the claim language of claim 1, only polypeptides which actually

comprise the **entire contiguous sequence** of SEQ ID NO:2 meet the claim limitations. While the claim encompasses polypeptides which may have additional amino acids flanking the amino acid sequence of SEQ ID NO:2, the claim does not encompass polypeptides which do not include the amino acid sequence of SEQ ID NO:2 , i.e. amino acid sequence variants of SEQ ID NO:2 which differ from SEQ ID NO:2 by 1 or more amino acids. Thus, naturally occurring allelic variants of SEQ ID NO:2, variants which are the translation of a single nucleotide polymorphism, or which have any conservative amino acid substitution, do not meet the claim limitations of claim 1. However, although the claims are considered indefinite, they have been examined based on the recited limitations.

The applicant argues that the claim 1 has been amended such that it no longer recites polypeptides which are at least 85% similar to SEQ ID NO:2. However, the grounds for lack of written description presented in the previous office action were not limited to a lack of written description for polypeptides which are at least 85% similar to SEQ ID NO:2. The previous office action also stated that the specification fails to provide an adequate written description for allelic variants of SEQ ID NO:2, or for variants of SEQ ID NO:2. Thus, applicant's argument that the amendment to claim 1 overcomes the instant grounds of rejection is not compelling.

The previous office action stated that the specification does not provide a sufficient written description for the scope of polypeptides encompassed by these claims. The specification discloses the isolation of a human cDNA , SEQ ID NO: 1, which contains an open reading frame comprising the amino acid sequence set forth in SEQ ID NO:2. The specification further discloses

that SEQ ID NO:2 shares > approximately 91% sequence homology to a sequence previously reported as human prothymosin α.. The specification however fails to provide a sufficient description of a protein with the amino acid sequence of SEQ ID NO:2. The specification provides no description for any of the structural, physical, or biological properties of the putative protein corresponding to SEQ ID NO:2. Aside from the putative amino acid sequence, the specification provides no evidence that any polypeptide corresponding to the predicted amino acid sequence is in fact produced naturally in any type of cell or that the predicted protein product has any biological activity. The specification further fails to provide any guidance as to the characteristics of the putative protein such as cellular location, stability, half-life, or protein interactions such that allelic variants which share these properties can be identified. The specification further fails to provide any evidence of naturally occurring allelic variants of SEQ ID NO:2 which have only a single amino acid polymorphism. Applicant's amendment does not overcome this issue as claim 2-4 continue to recite naturally occurring allelic variants of SEQ ID NO:2 and single amino acid variants of SEQ ID NO:2.

In regards to the disclosed homology between SEQ ID NO:2 and human prothymosin α , the art at the time of filing teaches that the human prothymosin α gene family contains 6 known members. Of these, one gene contains introns and is expressed in two alternately spliced forms, whereas the other 5 are considered pseudogenes whose expression has not been conclusively established (Pineiro et al., (2000), Peptides, Vol. 21, 1433-1446). The 6 known prothymosin α genes are highly conserved and share greater than 95% sequence homology. Pineiro et al. also

states that determination of pseudogene transcription and expression of the putative protein products of the pseudogenes is complicated by the degree of genomic conservation and apparent absence of size heterogeneity (Piniero et la., page 1436, column 2). Thus, based on the teachings of the art at the time of filing, the skilled artisan would not have been able to predict that a gene sequence with a high degree of homology to human prothymosin α would in fact encode a functional human prothymosin α polypeptide. Furthermore, while the specification provides data from an RT-PCR assay which demonstrates the detection of mRNA transcripts in various cell types using PCR primers derived from SEQ ID NO:1, the specification provides no evidence that these mRNA are in fact translated into functional protein, or that the putative protein produced shares any of the properties or characteristics of human prothymosin α . Absent factual evidence, a percentage sequence similarity of less than 100% is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a known biomolecule with a similar sequence. It is known for nucleic acids as well as for proteins that even a single nucleotide or amino acid change or mutation can destroy or substantially change the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones will have a significant effect on structure, folding, activity etc. Therefore, the recitation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed polypeptides and the human prothymosin α protein in terms of biological properties and functions. Several publications document the unpredictability of attributing function based on sequence similarity. See in particular Gerhold et al. (1996)

BioEssays, Vol. 18, No. 12, 973-981, Wells et al. (1997) J. Leuk. Biol., Vol. 61 (5), 545-550, and Russell et al. (1994) J. Mol. Biol., Vol. 244, 322-350. Thus, in the absence of any specific teachings in the specification concerning actual biological properties such as tissue distribution, expression, and function of polypeptides comprising SEQ ID NO:2, the lack of description of any naturally occurring allelic variant of SEQ ID NO:2, and in view of the art recognized unpredictability of attributing particular functional properties to a polypeptide based on sequence similarity and the art recognized existence of untranslated pseudogenes with greater than 95% sequence homology to human prothymosin α , the specification fails to meet the requirements for written description under 35 U.S.C. 112, first paragraph.

The applicant is reminded that *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Please note as well that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

The rejection of claims 1-4, 23-24, 29, and 32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention as claimed, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Under the heading entitled, Enablement, the applicant has provided arguments directed solely to a rejection of the claims under 35 U.S.C. 101 for lack of utility. The applicant quotes form the Utility Examination Guidelines provided in the Federal Register and states that the applicants have asserted a specific, substantial, and/or credible utility for the disclosed polypeptides. However**, the office has not made a rejection of the claims under 35 U.S.C. 101 for lack of utility**. The rejection of record over the instant claims is an enablement rejection under 35 U.S.C. 112, first paragraph. The standards for determining utility under 35 U.S.C. 101 as discussed in the Utility Examination Guidelines provided in the Federal Register (Fed. Reg., Vol. 66, No. 4, January 5, 2001) are not the same as the standards used to determine whether a specification provides an enabling disclosure for how to make and use the invention as claimed. Therefore, applicant's arguments regarding utility as discussed in the Utility Examination Guidelines do not apply to the instant rejection of the claims under 35 U.S.C. 112, first paragraph, for lack of enablement.

The previous office action discussed the fact that the specification fails to provide sufficient guidance as to the structural and biological properties of the putative protein corresponding to SEQ ID NO:2, or provide guidance as to naturally occurring allelic variants of SEQ ID NO:2. The specification further fails to identify amino acid residues of SEQ ID NO:2 or nucleic acid sequences of SEQ ID NO:1 which are either crucial or non-essential for the biological activity of the putative protein such that the skilled artisan could predict without undue experimentation which amino acids or nucleotides could be altered without affecting protein folding, stability, and biological activity.

While the specification notes the high degree of sequence similarity between the putative protein corresponding to SEQ ID NO:2 and human prothymosin α , and provides a working examples which demonstrates detection of mRNA in cells using primers derived from SEQ ID NO:1, the specification fails to provide any specific evidence that SEQ ID NO:1 encodes a protein corresponding to SEQ ID NO:2 or provide any specific guidance as to the particular biological activity of a putative protein encoded by SEQ ID NO:1, which is alleged to be the amino acid sequence of SEQ ID NO:2. The specification also fails to provide sufficient guidance that a protein corresponding to SEQ ID NO:2 shares any biological activity in common with prothymosin α. At the time of filing, the art teaches that while the actual intracellular role of prothymosin α remains undefined, human prothymosin α may play a role in cellular proliferation and is capable of immunomodulatory activity (Piniero et al., page 1438, column 1). However, the specification provides no evidence that the polypeptide encoded by SEQ ID NO:1, or the amino

acid sequence of SEQ ID NO:2 is capable of mediating any effect on cellular proliferation or capable of mediating any type of immunomodulatory activity. It is also noted that at the time of filing the art teaches that the human prothymosin α gene family contains numerous pseudogenes with greater than 95% sequence similarity to human prothymosin α whose translation and function has not been conclusively demonstrated in cells either *in vitro* or *in vivo*. Thus, in view of the lack of guidance concerning any biological property of a protein corresponding to the amino acid sequence of SEQ ID NO:2 or encoded by SEQ ID NO:1, the absence of evidence in the specification that the amino acid sequence of SEQ ID NO:2 shares any biological activities in common with prothymosin α, the presence of numerous unexpressed pseudogenes in the prothymosin α gene family, the lack of guidance as to functional domains and amino acids critical for biological activity in the putative protein of SEQ ID NO:2, and the breadth of the claims, the skilled artisan at the time of filing would not have been able to predict whether a protein with an amino acid sequence corresponding to SEQ ID NO:2, or a protein with 85% or greater sequence identity with SEQ ID NO:2 would have any type of biological activity in cells *in vitro* or *in vivo*.

In addition, the specification fails to provide any guidance as to pathologies or diseases associated with the putative polypeptide corresponding to SEQ ID NO:2. Based on the known activities of prothymosin α, the specification hypothesizes that polypeptides of the instant invention would be useful for treating conditions related to cellular proliferation, such as cancer. However, it is noted that neither the prior art nor the specification actually identifies any pathology or disease which is directly affected by the expression or lack of expression of any

prothymosin α gene or protein. Further, as discussed in detail above, the specification fails to provide any evidence that a putative polypeptide corresponding to SEQ ID NO:2 actually shares any biological activity in common with prothymosin α. The specification also fails to provide any guidance for treating cancer using the putative protein corresponding to SEQ ID NO:2. The specification does not provide any guidance as to the properties or activities of the SEQ ID NO:2 polypeptide that would suggest that the addition of a polypeptide corresponding to SEQ ID NO:2 to cancer cells would result in any effect on cancer growth or metastasis. The applicant is reminded that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) . In the absence of specific information as to the actual biological properties of a polypeptide corresponding to SEQ ID NO:2 and the identity of diseases or conditions which are directly attributable to the expression or lack of expression of a polypeptide corresponding to SEQ ID NO:2, and in view of the lack of working examples demonstrating any therapeutic effect on any disease or pathology following the administration of a polypeptide corresponding to SEQ ID NO:2 and the breath of the claims, it would have required undue experimentation for the skilled artisan to identify and treat any disease associated with the putative polypeptide corresponding to SEQ ID NO:2.

Please note that the Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence

or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the instant finding of a lack of enablement. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Ultimately, ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The rejection of claim 35 under 35 U.S.C. 112, second paragraph, and 35 U.S.C. 101, is withdrawn in view of the cancellation of the claim.

Applicant's amendments to the claims has resulted in the following new grounds of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 22-23, 29, and 32 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2-4, 22-23, 29, and 32 all depend ultimately on claim 1. Claim 1 has been amended to recite, "An isolated polypeptide comprising an amino acid sequence of SEQ ID NO:2." The term "comprising" is considered open claim language. Thus, Claim 1 is interpreted to encompass a polypeptide which consists of SEQ ID NO:2 and to further encompass polypeptides which include SEQ ID NO:2 and additional flanking amino acids. The claim as written does not encompass polypeptides which comprise an amino acid sequence similar to SEQ ID NO:2 but which differs from that sequence by 1 or more amino acids. In view of the amendment to claim 1, claims 2-4, which recite the polypeptide of claim 1 which is a naturally occurring allelic variant or variant polypeptide which has a conservative amino acid substitution or which is the translation of a single nucleotide polymorphism, are confusing and contradictory. Since the limitations of claim 2-4 contradict the limitations of claim 1, the metes and bounds of claim 1-4, and claims 23-24, 29, and 32, which depend on claim1, cannot be determined.

Claim 4 is further indefinite for the recitation of " ....a variant polypeptide described therein, wherein any amino acid specified in the chosen sequence ...." . Claim 4 depends on claim 1, which as discussed above recites a polypeptide comprising the amino acid sequence of SEQ ID NO:2. Claim 1 does not provide any antecedent basis for "the variant polypeptide described

therein". Further, claim 1 does not specify any amino acid for substitution or recite any "chosen sequence". As such, the metes and bounds of the "variant polypeptide", the "chosen sequence", and the "amino acid specified", cannot be determined.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 4, 23-24, 29, 32, and 35 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,659,694 (Horecker) is withdrawn in view of applicant's cancellation or amendment to the claims.

The rejection of claims 1, 4, 23-24, 29, 32, and 35 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,716,148 (Horecker) is withdrawn in view of applicant's cancellation or amendment to the claims.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER